Bibliography

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Placental Growth Factor (PlGF) in first trimester of pregnancy

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First-trimester prediction of hypertensive disorders in pregnancy.

Poon LC, Kametas NA, Maiz N, Akolekar R, Nicolaides KH.

Hypertension. 2009 May;53(5):812-8. Epub 2009 Mar 9.

This study aimed to establish a method of screening for pregnancy hypertension by a combination of maternal variables, including mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A, and placental growth factor in early pregnancy. The base-cohort population constituted of 7797 singleton pregnancies, including 34 case subjects who developed preeclampsia (PE) requiring delivery before 34 weeks (early PE) and 123 with late PE, 136 with gestational hypertension, and 7504 cases subjects (96.3%) who were unaffected by PE or gestational hypertension. Maternal history, uterine artery pulsatility index, mean arterial pressure, and pregnancy-associated plasma protein-A were recorded in all of the cases in the base cohort, but placental growth factor was measured only in the case-control population of 209 cases who developed hypertensive disorders and 418 controls. In each case the measured mean arterial pressure, uterine artery pulsatility index, pregnancy-associated plasma protein-A, and placental growth factor were converted to a multiple of the expected median (MoM) after correction for maternal characteristics found to affect the measurements in the unaffected group. Early PE and late PE were associated with increased mean arterial pressure (1.15 MoM and 1.08 MoM) and uterine artery pulsatility index (1.53 MoM and 1.23 MoM) and decreased pregnancy-associated plasma protein-A (0.53 MoM and 0.93 MoM) and placental growth factor (0.61 MoM and 0.83 MoM). Logistic regression analysis was used to derive algorithms for the prediction of hypertensive disorders. It was estimated that, with the algorithm for early PE, 93.1%, 35.7%, and 18.3% of early PE, late PE, and gestational hypertension, respectively, could be detected with a 5% false-positive rate and that 1 in 5 pregnancies classified as being screen positive would develop pregnancy hypertension. This method of screening is far superior to the traditional approach, which relies entirely on maternal history.

First trimester urinary placental growth factor and development of pre-eclampsia.

Savvidou MD, Akolekar R, Zaragoza E, Poon LC, Nicolaides KH.

BJOG. 2009 Apr;116(5):643-7. Epub 2009 Feb 10.

OBJECTIVE: To compare urinary placental growth factor (PlGF) concentration at 11(+0) to 13(+6) weeks of gestation in women who subsequently develop pre-eclampsia with normotensive controls. DESIGN: Nested case-control study within a prospective study for first trimester prediction of pre-eclampsia.

SETTING: Routine antenatal visit in a teaching hospital.

POPULATION: Fifty-two women who developed pre-eclampsia and 52 controls matched for gestational age and sample storage time.

METHODS: Urinary PlGF concentration and PlGF to creatinine ratio were measured in women who developed pre-eclampsia and their matched controls. Comparisons between groups were performed using Student's t test.

MAIN OUTCOME MEASURES: Development of pre-eclampsia.

RESULTS: In the pre-eclampsia group, the median urinary PlGF concentration (20.6 pg/ml, interquartile range [IQR] 9.1-32.0 pg/ml) and median urinary PlGF to creatinine ratio (1.6 pg/mg, IQR 1.2-2.5 pg/mg) were not significantly different from the control group (11.8 pg/ml, IQR 5.5-29.8 pg/ml, P=0.1 and 1.7 pg/mg, IQR 1.2-2.3 pg/mg, P=0.3, respectively). There were no significant differences between women with early-onset pre-eclampsia requiring delivery before 34 weeks (n=13) and those with late-onset pre-eclampsia (n=39) and between women with pre-eclampsia and fetal growth restriction (FGR) (n=25) and those with pre-eclampsia and no FGR (n=27) in either median PlGF concentration or median urinary PlGF to creatinine ratio.

CONCLUSIONS: The development of pre-eclampsia is not preceded by altered urinary PlGF concentration in the first trimester of pregnancy.

Maternal serum placental growth factor (PlGF) in small for gestational age pregnancy at 11(+0) to 13(+6) weeks of gestation.

Poon LC, Zaragoza E, Akolekar R, Anagnostopoulos E, Nicolaides KH.

Prenat Diagn. 2008 Dec;28(12):1110-5.

OBJECTIVE: To investigate the pathogenesis of pregnancies delivering small for gestational age (SGA) neonates by examining biochemical and Doppler indices of placental development during the first trimester of pregnancy.

METHOD: The concentration of placental growth factor (PlGF) at 11(+0)-13(+6) weeks was measured in 296 cases, which delivered SGA neonates, and 609 controls. The newborn was considered to be SGA if the birth weight was less than the fifth percentile after correction for gestation at delivery and sex, maternal racial origin, weight, height and parity. The distributions of uterine artery pulsatility index (PI), PlGF and PAPP-A, expressed in multiples of the median (MoM), in the control and SGA groups were compared. Logistic regression analysis was used to determine if significant contribution is provided by maternal factors, PlGF, PAPP-A and uterine artery PI in predicting SGA.

RESULTS: The median PlGF (0.900 MoM) and PAPP-A (0.778 MoM) were lower and uterine artery PI was higher (1.087 MoM) in the SGA group than in the controls (PlGF: 0.991 MoM; PAPP-A: 1.070 MoM; uterine artery PI: 1.030 MoM). In the SGA group there was a significant association between PlGF and PAPP-A ($r = 0.368$, $p < 0.0001$) and uterine artery PI ($r = 0.191$, $p = 0.001$). Significant contributions for the prediction of SGA were provided by maternal factors, PlGF and PAPP-A and with combined screening the detection rate was 27% at a false-positive rate of 5%.

CONCLUSION: Birth weight is predetermined by placental development during the first trimester of pregnancy.

Maternal serum placental growth factor at 11 + 0 to 13 + 6 weeks of gestation in the prediction of pre-eclampsia.

Akolekar R, Zaragoza E, Poon LC, Pepes S, Nicolaides KH.

Ultrasound Obstet Gynecol. 2008 Nov;32(6):732-9.

OBJECTIVE: To investigate the potential value of maternal serum placental growth factor (PlGF) in first-trimester screening for pre-eclampsia (PE).

METHODS: The concentration of PlGF at 11 + 0 to 13 + 6 weeks' gestation was measured in samples from 127 pregnancies that developed PE, including 29 that required delivery before 34 weeks (early PE) and 98 with late PE, 88 cases of gestational hypertension (GH) and 609 normal controls. The distributions of PlGF multiples of the median (MoM) in the control and hypertensive groups were compared. Logistic regression analysis was used to determine the factors with a significant contribution for predicting PE.

RESULTS: In the control group significant independent contributions for log PlGF were provided by fetal crown-rump length, maternal weight, cigarette smoking and racial origin, and after correction for these variables the median MoM PlGF was 0.991. In the early-PE and late-PE groups PlGF (0.611 MoM and 0.822 MoM, respectively; $P < 0.0001$) and pregnancy-associated plasma protein-A (PAPP-A) (0.535 MoM; $P < 0.0001$ and 0.929 MoM; $P = 0.015$, respectively) were reduced but in GH (PlGF: 0.966 MoM; PAPP-A: 0.895 MoM) there were no significant differences from controls. Significant contributions for the prediction of PE were provided by maternal characteristics and obstetric history, serum PlGF and uterine artery pulsatility index (PI) and with combined screening the detection rates for early PE and late PE were 90% and 49%, respectively, for a false-positive rate of 10%.

CONCLUSION: Effective screening for PE can be provided by a combination of maternal characteristics and obstetric history, uterine artery PI and maternal serum PlGF at 11 + 0 to 13 + 6 weeks' gestation. (c) 2008 ISUOG. Published by John Wiley & Sons, Ltd.

Serum inhibin A and angiogenic factor levels in pregnancies with previous preeclampsia and/or chronic hypertension: are they useful markers for prediction of subsequent preeclampsia?

Sibai BM, Koch MA, Freire S, Pinto e Silva JL, Rudge MV, Martins-Costa S, Bartz J, de Barros Santos C, Cecatti JG, Costa R, Ramos JG, Spinnato JA 2nd.
Am J Obstet Gynecol. 2008 Sep;199(3):268.e1-9.

OBJECTIVE: Our objective was to determine whether measurement of placenta growth factor (PLGF), inhibin A, or soluble fms-like tyrosine kinase-1 (sFlt-1) at 2 times during pregnancy would usefully predict subsequent preeclampsia (PE) in women at high risk.

STUDY DESIGN: We analyzed serum obtained at enrollment (12(0/7) to 19(6/7) weeks) and follow-up (24-28 weeks) from 704 patients with previous PE and/or chronic hypertension (CHTN) enrolled in a randomized trial for the prevention of PE. Logistic regression analysis assessed the association of log-transformed markers with subsequent PE; receiver operating characteristic analysis assessed predictive value.

RESULTS: One hundred four developed preeclampsia: 27 at 37 weeks or longer and 77 at less than 37 weeks (9 at less than 27 weeks). None of the markers was associated with PE at 37 weeks or longer. Significant associations were observed between PE at less than 37 weeks and reduced PLGF levels at baseline ($P = .022$) and follow-up ($P < .0001$) and elevated inhibin A ($P < .0001$) and sFlt-1 ($P = .0002$) levels at follow-up; at 75% specificity, sensitivities ranged from 38% to 52%. Using changes in markers from baseline to follow-up, sensitivities were 52-55%. Associations were observed between baseline markers and PE less than 27 weeks ($P <$ or $= .0004$ for all); sensitivities were 67-89%, but positive predictive values (PPVs) were only 3.4-4.5%.

CONCLUSION: Inhibin A and circulating angiogenic factors levels obtained at 12(0/7) to 19(6/7) weeks have significant associations with onset of PE at less than 27 weeks, as do levels obtained at 24-28 weeks with onset of PE at less than 37 weeks. However, because the corresponding sensitivities and/or PPVs were low, these markers might not be clinically useful to predict PE in women with previous PE and/or CHTN.

The change in concentrations of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters in risk assessment for the subsequent development of preeclampsia and small-for-gestational age.

Erez O, Romero R, Espinoza J, Fu W, Todem D, Kusanovic JP, Gotsch F, Edwin S, Nien JK, Chaiworapongsa T, Mittal P, Mazaki-Tovi S, Than NG, Gomez R, Hassan SS.

J Matern Fetal Neonatal Med. 2008 May;21(5):279-87.

INTRODUCTION: An imbalance between angiogenic and anti-angiogenic factors has been proposed as central to the pathophysiology of preeclampsia (PE). Indeed, patients with PE and those delivering small-for-gestational age (SGA) neonates have higher plasma concentrations of soluble vascular endothelial growth factor receptor-1 (sVEGFR-1) and the soluble form of endoglin (s-Eng), as well as lower plasma concentrations of vascular endothelial growth factor (VEGF) and placental growth factor (PlGF) than do patients with normal pregnancies. Of note, this imbalance has been observed before the clinical presentation of PE or the delivery of an SGA neonate. The objective of this study was to determine if changes in the profile of angiogenic and anti-angiogenic factors in maternal plasma between the first and second trimesters are associated with a high risk for the subsequent development of PE and/or delivery of an SGA neonate.

METHODS: This longitudinal case-control study included 402 singleton pregnancies in the following groups: (1) normal pregnancies with appropriate for gestational age (AGA) neonates (n = 201); (2) patients who delivered an SGA neonate (n = 145); and (3) patients who developed PE (n = 56). Maternal plasma samples were obtained at the time of each prenatal visit, scheduled at 4-week intervals from the first or early second trimester until delivery. In this study, we included two samples per patient: (1) first sample obtained between 6 and 15 weeks of gestation ('first trimester' sample), and (2) second sample obtained between 20 and 25 weeks of gestation ('second trimester' sample). Plasma concentrations of s-Eng, sVEGFR-1, and PlGF were determined by specific and sensitive immunoassays. Changes in the maternal plasma concentrations of these angiogenesis-related factors were compared among normal patients and those destined to develop PE or deliver an SGA neonate while adjusting for maternal age, nulliparity, and body mass index. General linear models and polytomous logistic regression models were used to relate the analyte concentrations, ratios, and product to the subsequent development of PE and SGA.

RESULTS: (1) An increase in the maternal plasma concentration of s-Eng between the first and second trimesters conferred risk for the development of preterm PE and SGA (OR 14.9, 95% CI 4.9-45.0 and OR 2.9, 95% CI 1.5-5.6, respectively). (2) An increase in the maternal plasma concentration of sVEGFR-1 between the first and second trimester conferred risk for the development of preterm PE (OR 3.9, 95% CI 1.2-12.6). (3) A subnormal increase in maternal plasma PlGF concentration between the first and the second trimester was a risk factor for the subsequent development of preterm and

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term PE (OR 4.3, 95% CI 1.2-15.5 and OR 2.7, 95% CI 1.2-5.9, respectively). (4) In addition, the combination of the three analytes into a pro-angiogenic versus anti-angiogwenic ratio (PlGF/(s-Eng x VEGFR-1)) conferred risk for the subsequent development of preterm PE (OR 3.7, 95% CI 1.1-12.1). (5) Importantly, patients with a high change in the s-Eng x sVEGFR-1 product had an OR of 10.4 (95% CI 3.2-33.8) for the development of preterm PE and 1.6 (95% CI 1.0-2.6) for the development of SGA.

CONCLUSIONS: Changes in the maternal plasma concentrations of s-Eng, sVEGFR-1, PlGF or their ratios between the first and second trimesters of pregnancy confer an increased risk to deliver an SGA neonate and/or develop PE.

A longitudinal study of angiogenic (placental growth factor) and anti-angiogenic (soluble endoglin and soluble vascular endothelial growth factor receptor-1) factors in normal pregnancy and patients destined to develop preeclampsia and deliver a small for gestational age neonate.

Romero R, Nien JK, Espinoza J, Todem D, Fu W, Chung H, Kusanovic JP, Gotsch F, Erez O, Mazaki-Tovi S, Gomez R, Edwin S, Chaiworapongsa T, Levine RJ, Karumanchi SA.

J Matern Fetal Neonatal Med. 2008 Jan;21(1):9-23.

INTRODUCTION: Accumulating evidence suggests that an imbalance between pro-angiogenic (i.e., vascular endothelial growth factor (VEGF) and placental growth factor (PlGF)) and anti-angiogenic factors (i.e., soluble VEGF receptor-1 (sVEGFR-1, also referred to as sFlt1)) is involved in the pathophysiology of preeclampsia (PE). Endoglin is a protein that regulates the pro-angiogenic effects of transforming growth factor beta, and its soluble form has recently been implicated in the pathophysiology of PE. The objective of this study was to determine if changes in maternal plasma concentration of these angiogenic and anti-angiogenic factors differ prior to development of disease among patients with normal pregnancies and those destined to develop PE (preterm and term) or to deliver a small for gestational age (SGA) neonate.

METHODS: This longitudinal nested case-control study included 144 singleton pregnancies in the following groups: (1) patients with uncomplicated pregnancies who delivered appropriate for gestational age (AGA) neonates (n = 46); (2) patients who delivered an SGA neonate but did not develop PE (n = 56); and (3) patients who developed PE (n = 42). Longitudinal samples were collected at each prenatal visit, scheduled at 4-week intervals from the first or early second trimester until delivery. Plasma concentrations of soluble endoglin (s-Eng), sVEGFR-1, and PlGF were determined by specific and sensitive ELISA.

RESULTS: (1) Patients destined to deliver an SGA neonate had higher plasma concentrations of s-Eng throughout gestation than those with normal pregnancies; (2) patients destined to develop preterm PE and term PE had significantly higher concentrations of s-Eng than those with normal pregnancies at 23 and 30 weeks, respectively (for preterm PE: $p < 0.036$ and for term PE: $p = 0.002$); (3) patients destined to develop PE (term or preterm) and those who delivered an SGA neonate had lower plasma concentrations of PlGF than those with a normal pregnancy throughout gestation, and the maternal plasma concentration of this analyte became detectable later among patients with pregnancy complications, compared to normal pregnant women; (4) there were no significant differences in the plasma concentrations of sVEGFR-1 between patients destined to deliver an SGA neonate and those with normal pregnancies; (5) patients destined to develop preterm and term PE had a significantly higher plasma concentration of sVEGFR-1 at 26 and 29 weeks of gestation than controls ($p = 0.009$ and $p = 0.0199$, respectively); and (6) there was no significant difference in the increment of sVEGFR-1 between control patients and those who delivered an SGA neonate ($p = 0.147$ at 25 weeks and $p = 0.8285$ at 40 weeks).

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CONCLUSIONS: (1) Changes in the maternal plasma concentration of s-Eng, sVEGFR-1, and PlGF precede the clinical presentation of PE, but only changes in s-Eng and PlGF precede the delivery of an SGA neonate; and (2) differences in the profile of angiogenic and anti-angiogenic response to intrauterine insults may determine whether a patient will deliver an SGA neonate, develop PE, or both.

Circulating angiogenic factors in early pregnancy and the risk of preeclampsia, intrauterine growth restriction, spontaneous preterm birth, and stillbirth.

Smith GC, Crossley JA, Aitken DA, Jenkins N, Lyall F, Cameron AD, Connor JM, Dobbie R.
Obstet Gynecol. 2007 Jun;109(6):1316-24.

OBJECTIVE: To estimate the relationship between maternal serum levels of placental growth factor (PlGF) and soluble fms-like tyrosine kinase-1 (sFlt-1) in early pregnancy with the risk of subsequent adverse outcome.

METHODS: A nested, case-control study was performed within a prospective cohort study of Down syndrome screening. Maternal serum levels of sFlt-1 and PlGF at 10-14 weeks of gestation were compared between 939 women with complicated pregnancies and 937 controls. Associations were quantified as the odds ratio for a one decile increase in the corrected level of the analyte.

RESULTS: Higher levels of sFlt-1 were not associated with the risk of preeclampsia but were associated with a reduced risk of delivery of a small for gestational age infant (odds ratio [OR] 0.92, 95% confidence interval [CI] 0.88-0.96), extreme (24-32 weeks) spontaneous preterm birth (OR 0.90, 95% CI 0.83-0.99), moderate (33-36 weeks) spontaneous preterm birth (OR 0.93, 95% CI 0.88-0.98), and stillbirth associated with abruption or growth restriction (OR 0.77, 95% CI 0.61-0.95). Higher levels of PlGF were associated with a reduced risk of preeclampsia (OR 0.95, 95% CI 0.90-0.99) and delivery of a small for gestational age infant (OR 0.95, 95% CI 0.91-0.99). Associations were minimally affected by adjustment for maternal characteristics.

CONCLUSION: Higher early pregnancy levels of sFlt-1 and PlGF were associated with a decreased risk of adverse perinatal outcome.

Changes in circulating level of angiogenic factors from the first to second trimester as predictors of preeclampsia.

Vatten LJ, Eskild A, Nilsen TI, Jeansson S, Jenum PA, Staff AC.
Am J Obstet Gynecol. 2007 Mar;196(3):239.e1-6.

OBJECTIVE: This study was undertaken to assess changes in placenta growth factor and soluble fms-like tyrosine kinase-1 as predictors of preeclampsia.

STUDY DESIGN: Nested case-control study of 154 preeclampsia cases delivered preterm and 190 delivered at term, and 392 controls.

RESULTS: Comparing the lowest and highest quartile of placenta growth factor increase from first to second trimester, the odds for preterm preeclampsia was 13.8 (95% CI, 4.4-43.2) higher for women with the lowest increase. Compared with controls, women with preterm preeclampsia had lower soluble fms-like tyrosine kinase-1 in the first, but higher in second trimester. Comparing highest and lowest quartile of increase, the odds for preterm preeclampsia was 9.2 (95% CI 3.4-25.0) higher for women with highest increase. Low placenta growth factor and high soluble fms-like tyrosine kinase-1 increase combined yielded extremely high relative risk of preterm preeclampsia (odds ratio, 35.3, 95% CI, 7.6-164.2), compared with the combination of high (placenta growth factor) and low (soluble fms-like tyrosine kinase-1) increase.

CONCLUSION: Low placenta growth factor and high soluble fms-like tyrosine kinase-1 increase from first to second trimester are strong predictors of preeclampsia.

Circulating angiogenic factors and the risk of preeclampsia.

Levine RJ, Maynard SE, Qian C, Lim KH, England LJ, Yu KF, Schisterman EF, Thadhani R, Sachs BP, Epstein FH, Sibai BM, Sukhatme VP, Karumanchi SA.

N Engl J Med. 2004 Feb 12;350(7):672-83. Epub 2004 Feb 5

BACKGROUND: The cause of preeclampsia remains unclear. Limited data suggest that excess circulating soluble fms-like tyrosine kinase 1 (sFlt-1), which binds placental growth factor (PlGF) and vascular endothelial growth factor (VEGF), may have a pathogenic role.

METHODS: We performed a nested case-control study within the Calcium for Preeclampsia Prevention trial, which involved healthy nulliparous women. Each woman with preeclampsia was matched to one normotensive control. A total of 120 pairs of women were randomly chosen. Serum concentrations of angiogenic factors (total sFlt-1, free PlGF, and free VEGF) were measured throughout pregnancy; there were a total of 655 serum specimens. The data were analyzed cross-sectionally within intervals of gestational age and according to the time before the onset of preeclampsia.

RESULTS: During the last two months of pregnancy in the normotensive controls, the level of sFlt-1 increased and the level of PlGF decreased. These changes occurred earlier and were more pronounced in the women in whom preeclampsia later developed. The sFlt-1 level increased beginning approximately five weeks before the onset of preeclampsia. At the onset of clinical disease, the mean serum level in the women with preeclampsia was 4382 pg per milliliter, as compared with 1643 pg per milliliter in controls with fetuses of similar gestational age ($P<0.001$). The PlGF levels were significantly lower in the women who later had preeclampsia than in the controls beginning at 13 to 16 weeks of gestation (mean, 90 pg per milliliter vs. 142 pg per milliliter, $P=0.01$), with the greatest difference occurring during the weeks before the onset of preeclampsia, coincident with the increase in the sFlt-1 level. Alterations in the levels of sFlt-1 and free PlGF were greater in women with an earlier onset of preeclampsia and in women in whom preeclampsia was associated with a small-for-gestational-age infant.

CONCLUSIONS: Increased levels of sFlt-1 and reduced levels of PlGF predict the subsequent development of preeclampsia.

Correlations of placental perfusion and PlGF protein expression in early human pregnancy.

Welch PC, Amankwah KS, Miller P, McAsey ME, Torry DS.

Am J Obstet Gynecol. 2006 Jun;194(6):1625-9; discussion 1629-31. Epub 2006 Apr 25.

OBJECTIVE: The purpose of this study was to investigate temporal correlations between maternal serum placenta growth factor levels and placental perfusion in early human pregnancies.

STUDY DESIGN: Systolic umbilical artery Doppler blood flow velocity indices at fetal and placental insertion sites were measured between 7 and 22 weeks of gestation from normal singleton pregnancies. Maternal serum placenta growth factor levels were determined by enzyme-linked immunosorbent assay.

RESULTS: Maternal serum placenta growth factor levels showed an exponential increase at approximately 14 weeks of gestation. Placenta perfusion, as estimated by systolic Doppler blood flow indices, significantly increased with gestational age ($P < .0001$). There was a close association between placenta growth factor expression levels and evidence of increased placenta perfusion ($P < .033$).

CONCLUSION: The significant increase in serum placenta growth factor coincides with the increased perfusion of the maternal/fetal interface at approximately 12 to 14 weeks of gestation. Correlation of placenta growth factor expression and placental perfusion suggests that placenta growth factor may contribute to assuring adequate vascular development/function of the placenta early in gestation.

Insulin resistance and alterations in angiogenesis: additive insults that may lead to preeclampsia.

Thadhani R, Ecker JL, Mutter WP, Wolf M, Smirnakis KV, Sukhatme VP, Levine RJ, Karumanchi SA.

Hypertension. 2004 May;43(5):988-92. Epub 2004 Mar 15.

Altered angiogenesis and insulin resistance, which are intimately related at a molecular level, characterize preeclampsia. To test if an epidemiological interaction exists between these two alterations, we performed a nested case-control study of 28 women who developed preeclampsia and 57 contemporaneous controls. Serum samples at 12 weeks of gestation were measured for sex hormone binding globulin (SHBG; low levels correlate with insulin resistance) and placental growth factor (PlGF; a proangiogenic molecule). Compared with controls, women who developed preeclampsia had lower serum levels of SHBG (208+/-116 versus 256+/-101 nmol/L, P=0.05) and PlGF (16+/-14 versus 67+/-150 pg/mL, P<0.001), and in multivariable analysis, women with serum levels of PlGF < or =20 pg/mL had an increased risk of developing preeclampsia (odds ratio [OR] 7.6, 95% CI 1.4 to 38.4). Stratified by levels of serum SHBG (< or =175 versus >175 mg/dL), women with low levels of SHBG and PlGF had a 25.5-fold increased risk of developing preeclampsia (P=0.10), compared with 1.8 (P=0.38) among women with high levels of SHBG and low levels of PlGF. Formal testing for interaction (PlGFxSHBG) was significant (P=0.02). In a model with 3 (n-1) interaction terms (high PlGF and high SHBG, reference), the risk for developing preeclampsia was as follows: low PlGF and low SHBG, OR 15.1, 95% CI 1.7 to 134.9; high PlGF and low SHBG, OR 4.1, 95% CI 0.45 to 38.2; low PlGF and high SHBG, OR 8.7, 95% CI 1.2 to 60.3. Altered angiogenesis and insulin resistance are additive insults that lead to preeclampsia.

First trimester placental growth factor and soluble fms-like tyrosine kinase 1 and risk for preeclampsia.

Thadhani R, Mutter WP, Wolf M, Levine RJ, Taylor RN, Sukhatme VP, Ecker J, Karumanchi SA.
J Clin Endocrinol Metab. 2004 Feb;89(2):770-5.

An imbalance of pro- and antiangiogenic factors may lead to preeclampsia (PE). In this prospective nested case-control study, we investigated whether first trimester serum levels of placental growth factor (PlGF), a potent angiogenic factor, and its soluble inhibitor, soluble fms-like tyrosine kinase 1 (sFlt1), distinguished women who developed PE (n = 40) from those who developed gestational hypertension (n = 40), delivered a small for gestational age (SGA) newborn (n = 40), or completed a full term normal pregnancy (n = 80). Compared with controls, serum PlGF levels were lower among women who developed PE (23 +/- 24 pg/ml vs. 63 +/- 145 pg/ml; P < 0.01) or gestational hypertension (27 +/- 19 pg/ml; P = 0.03), or who delivered a SGA newborn (21 +/- 16 pg/ml; P < 0.01). In contrast, serum sFlt1 levels did not markedly differ between the groups: PE, 1048 +/- 657 pg/ml; gestational hypertension, 942 +/- 437 pg/ml; SGA newborns, 1011 +/- 479 pg/ml; and normal controls, 973 +/- 490 pg/ml. Multivariable analysis adjusting for potential confounders and serum sFlt1 levels demonstrated a 3.7-fold (95% confidence interval, 1.2-12.5) increase in risk for PE for every log unit decrease in serum levels of PlGF compared with controls. Analyses for gestational hypertension and SGA were not significant. Examined in tertiles, the risk for PE was increased 28.7-fold (95% confidence interval, 2.3-351.0) in the third (<12 pg/ml) compared with the first (>39 pg/ml) PlGF tertile. First trimester serum levels of PlGF and sFlt1 may identify women at high risk for PE.

First-trimester maternal serum levels of placenta growth factor as predictor of preeclampsia and fetal growth restriction.

Ong CY, Liao AW, Cacho AM, Spencer K, Nicolaides KH.

Obstet Gynecol. 2001 Oct;98(4):608-11.
Comment in: Obstet Gynecol. 2001 Oct;98(4):596-9.

OBJECTIVE: To determine whether the reported decrease in maternal serum placenta growth factor concentration in preeclampsia is evident from the first trimester and before clinical onset of the disease. We also examined levels in pregnancies that subsequently resulted in fetal growth restriction (FGR).

METHODS: Placenta growth factor concentration was measured in stored maternal serum samples obtained at 11-14 weeks of gestation from 131 women who subsequently developed preeclampsia, 137 women who subsequently developed FGR, and 400 randomly selected controls who did not develop preeclampsia or FGR. Preeclampsia was defined as diastolic blood pressure of 90 mmHg or more on two occasions 4 hours apart, accompanied by proteinuria (more than 300 mg of total protein in a 24-hour urine collection or a positive test for albumin on reagent strip) in women with no pre-existing hypertensive or renal disease. Fetal growth restriction was considered present if a woman subsequently delivered a live infant with a birth weight below the fifth centile for gestation.

RESULTS: In the control group, maternal serum placenta growth factor concentration increased with gestation. Compared with the controls (median multiple of the median 0.98, standard deviation [SD] 0.51), levels in the preeclampsia group (median multiple of the median 1.09, SD 0.52) were not significantly different ($t = 1.83$, $P = .07$), but in the FGR group (median multiple of the median 1.57, SD 0.74), levels were significantly increased ($t = 10.85$, $P < .001$).

CONCLUSION: The previously reported decrease in serum placenta growth factor levels in women with preeclampsia might not precede clinical onset of the disease and is not apparent in the first trimester of pregnancy. Levels are significantly increased in pregnancies resulting in FGR.

Low maternal serum levels of placenta growth factor as an antecedent of clinical preeclampsia.

Tidwell SC, Ho HN, Chiu WH, Torry RJ, Torry DS.

Am J Obstet Gynecol. 2001 May;184(6):1267-72.

OBJECTIVE: Maternal serum placenta growth factor levels have been shown to be significantly reduced in women with established preeclampsia. However, the temporal change in serum placenta growth factor levels before the clinical onset of preeclampsia is not known.

STUDY DESIGN: Serum samples were collected from patients at the first prenatal (5-15 weeks' gestation), second-trimester (16-20 weeks' gestation), and third-trimester (26-30 weeks' gestation) visits. Serum placenta growth factor levels were determined and analyzed according to pregnancy outcome.

RESULTS: Maternal placenta growth factor levels during normal gestation increased dramatically from the first to the third trimester. At the same gestational time points, in contrast, significantly lower serum placenta growth factor levels were found in patients in whom mild or severe preeclampsia eventually developed ($P < .01$). Low maternal serum placenta growth factor levels during early gestation were associated with a significant odds ratio for development of preeclampsia ($P < .005$).

CONCLUSION: Relatively decreased levels of serum placenta growth factor occur before the onset of clinical preeclampsia, which suggests that placenta growth factor measurement could be used to discriminate those pregnancies predisposed to development of preeclampsia.

Maternal serum placental growth factor at 11-13 weeks in chromosomally abnormal pregnancies.

Zaragoza E, Akolekar R, Poon LC, Pepes S, Nicolaides KH.
Harris Birthright Research Centre for Fetal Medicine, King's College Hospital, London, UK.
Ultrasound Obstet Gynecol. 2009 Apr;33(4):382-6.

OBJECTIVES: To investigate the potential value of maternal serum placental growth factor (PlGF) in first-trimester screening for trisomy 21 and other major chromosomal abnormalities.

METHODS: The maternal serum concentration of PlGF at 11 + 0 to 13 + 6 weeks was measured in 609 euploid and 175 chromosomally abnormal pregnancies, including 90 with trisomy 21, 28 with trisomy 18, 19 with trisomy 13, 28 with Turner syndrome and 10 with triploidy. The levels of PlGF were compared in cases and controls, and were assessed for association with free beta-human chorionic gonadotropin (beta-hCG) and pregnancy-associated plasma protein-A (PAPP-A).

RESULTS: Logistic regression analysis demonstrated in the euploid group that significant independent contributions for log PlGF were provided by fetal crown-rump length, maternal weight, cigarette smoking and ethnic origin; after correction for these variables the median multiple of the median (MoM) PlGF was 0.991. Significantly lower values were observed in pregnancies with trisomy 21 (0.707 MoM), trisomy 18 (0.483 MoM), trisomy 13 (0.404 MoM), triploidy (0.531 MoM) and Turner syndrome (0.534 MoM). Significant contributions in the prediction of trisomy 21 were provided by maternal age, serum PlGF, PAPP-A and free beta-hCG, and the detection rates of screening with the combination of these variables were 70% and 80% at respective false-positive rates of 3% and 5%.

CONCLUSIONS: Maternal serum PlGF concentration at 11-13 weeks of gestation is potentially useful in first-trimester screening for trisomy 21 and other major chromosomal abnormalities. (c) 2009 ISUOG. Published by John Wiley & Sons, Ltd.

Circulating angiogenic proteins in trisomy 13.

Bdolah Y, Palomaki GE, Yaron Y, Bdolah-Abram T, Goldman M, Levine RJ, Sachs BP, Haddow JE, Karumanchi SA.

Am J Obstet Gynecol. 2006 Jan;194(1):239-45.

OBJECTIVE: Women who are carrying a trisomy 13 fetus are more prone to develop preeclampsia. Excess circulating soluble fms-like tyrosine kinase-1 has been implicated recently in the pathogenesis of preeclampsia. Since the fms-like tyrosine kinase-1/soluble fms-like tyrosine kinase-1 gene is located on chromosome 13q12, we hypothesized that the extra copy of this gene in trisomy 13 may lead to excess circulating soluble fms-like tyrosine kinase-1, reduced free placental growth factor level, and increased soluble fms-like tyrosine kinase-1/placental growth factor ratio. This may then contribute to the increased risk of preeclampsia that has been observed in these patients. Our objective was to characterize the maternal circulating angiogenic proteins in trisomy 13 pregnancies.

STUDY DESIGN: Maternal serum samples of trisomy 13, 18, 21 and normal karyotype pregnancies were obtained from first and second trimester screening programs. We chose 17 cases of trisomy 13 that were matched for maternal age, freezer storage time, and parity with 85 normal karyotype control samples. Additionally, 20 cases of trisomy 18 and 17 cases of trisomy 21 were included. Cases and control samples were assayed for levels of soluble fms-like tyrosine kinase-1 and placental growth factor by enzyme-linked immunosorbent assay in a blinded fashion. Because of the skewed distributions of soluble fms-like tyrosine kinase-1 and placental growth factor, nonparametric analytic techniques were used, and the results are reported as median and ranges.

RESULTS: In early pregnancy trisomy 13 cases and control samples, the median circulating soluble fms-like tyrosine kinase-1/placental growth factor ratios were 17.0 (range, 1.2-61.3) and 6.7 (range, 0.8-62.9), respectively (P = .003). The median soluble fms-like tyrosine kinase-1/placental growth factor ratios in trisomy 18 and 21 were 4.8 (range, 0.9-53.9) and 5.1 (range, 1.0-18.1), which were not significantly different than the control samples. Furthermore, the differences between trisomy 13 and control samples were more pronounced in the second trimester specimens than in the specimens from the first trimester.

CONCLUSION: These data suggest that alterations in circulating angiogenic factors may be involved intimately in the pathogenesis of preeclampsia in trisomy 13. A larger clinical study that measures these factors longitudinally and correlates them with pregnancy outcomes is needed to further establish the link between trisomy 13, altered angiogenic factors, and preeclampsia.

First trimester maternal serum placenta growth factor (PlGF) concentrations in pregnancies with fetal trisomy 21 or trisomy 18.

Spencer K, Liao AW, Ong CY, Geerts L, Nicolaides KH.

Prenat Diagn. 2001 Sep;21(9):718-22.

Placenta growth factor (PlGF), an angiogenic factor belonging to the vascular endothelial growth factor family, pregnancy-associated plasma protein A (PAPP-A) and free beta-human chorionic gonadotrophin (beta-hCG) were measured in maternal serum from 45 pregnancies with trisomy 21, 45 with trisomy 18 and 493 normal controls at 10-13 completed weeks of gestation. In the normal pregnancies maternal serum PlGF levels increased exponentially with gestation. The median multiple of the median (MoM) PlGF concentration in the trisomy 21 group (1.26 MoM) was significantly higher ($p<0.0001$) than in the control group (1.00 MoM). In the trisomy 18 group the median PlGF was lower (0.889 MoM) but this did not quite reach significance ($p=0.064$). The corresponding median MoM values for PAPP-A were 1.00 MoM for the controls, 0.49 MoM for trisomy 21 and 0.16 MoM for trisomy 18. The median MoM values for free beta-hCG were 1.00 MoM for the controls, 2.05 MoM for trisomy 21 and 0.38 MoM for trisomy 18. In the control group there was a small but significant correlation of PlGF with free beta-hCG ($r=+0.1024$) and PAPP-A ($r=+0.2288$). In the trisomy 18 group there was a significant association between PlGF and free beta-hCG ($r=+0.2629$) but not with PAPP-A ($r=+0.0038$). In the trisomy 21 group there was a small but significant association with PAPP-A ($r=+0.1028$) but not with free beta-hCG ($r=+0.0339$). The separation of affected and unaffected pregnancies in maternal serum PlGF is small, and therefore it is unlikely that measurement of PlGF would improve screening for these abnormalities provided by the combination of fetal nuchal translucency and maternal serum PAPP-A and free beta-hCG.

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